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Synthesis of Amino Derivatives of Dithio Acids as Potential Radiation Protective Agents

Annual Report

William O. Foye, Ph.D.

August 1984

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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07	05		

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

With the finding of appreciable radioprotective properties from quinolinium-2-dithioacetic acid derivatives, modifications in molecular structure were made to improve the stability properties of the molecules. Inclusion of hydroxy groups, additional amino groups, and a longer aliphatic chain in the amine moiety of the methylthio amino derivatives of the dithio acids was done, and stable compounds resulted in general. Use was made of 2-methylpyridine and 2,6-dimethylpyridine in place of 2-methylquinoline, and after N-methylation the corresponding bis(methylthio) and methylthio amino derivatives were prepared. The 2,6-dimethylpyridine allowed the preparation of a bis(dithioacetic acid) function not obtainable in the quinoline series. Several aminocycloalkenedithio acids were also prepared by literature procedures. The reaction of 1,2-dithiole-3-thiones with amines was investigated as a means of obtaining 3-amino-2-aryldithiopropenoate esters. The primary amine compound (formed from reaction with ammonia) was too unstable for testin but secondary amines gave stable products. Further work on the use of phthaloylamino-

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19. Abstract continued

alkanedithio acids was not successful in preparing the dephthaloylated dithio acids. Also, conversion of aminonitriles to amino dithio acids was unsuccessful. A stable copper (II) complex of the quinolinium-2-bis(methylthio)vinyl derivative was prepared and its structure proven. Screening data showed the bis(methylthio) and methylthio amino derivatives of the quinolinium-2-dithioacetic acids to have good (>50%) radioprotective activity at very low doses (<10mg/kg). Also, one of the amino-2-aryldithiopropenoates showed fair protective activity.

Summary

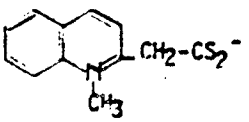
Appreciable radiation-protective properties were found with the N-methylquinolinium-2-dithioacetic acid derivatives. The bis(thiomethyl) and thiomethyl amino derivatives gave much greater protection (60-70% survival vs. 1000 rads) than the dithio acid zwitterion (20% survival), however. These derivatives were active at much lower dosage levels (2-10 mg/kg) than either the dithio acid zwitterion (75 mg/kg) or the amino thiols (150-600 mg/kg). To improve stability and distribution properties of these derivatives, inclusion of hydroxy and alkoxy functions, additional amino functions, and longer aliphatic chains in the amine portion of the methylthio amino derivatives was carried out. Also, the preparation of the corresponding N-methylpicoline derivatives was accomplished. Use of N-methyl-2,6-dimethylpyridine also allowed the synthesis of a bis(dithioacetic acid) function not obtainable in the quinoline series. Several aminocyclopentenedithio acids were prepared, and the reaction of 1,2-dithiole-3-thiones with amines was carried out, giving 3-amino-2-phenyldithiopropenoate esters. Other attempts to prepare aliphatic amine-containing dithio acids were unsuccessful, using literature procedures that apparently worked in the absence of amino groups.

Stable copper (II) complexes of the N-methylquinolinium-2-bis(methylthio)-vinyl and methylthio amino compounds were prepared and characterized. Since the bis(methylthio) and methylthio amino derivatives were radiation-protective at a much lower dose level than the amino thiols and have no transferable H atoms, it is probable that they are active by a different mechanism than that of the amino thiols.

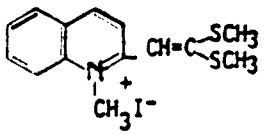
Table of Contents

Quinolinium-2-dithioacetic Acid Derivatives

With the finding of appreciable radioprotective properties from the quinolinium-2-dithioacetic acid derivatives (I-III), modifications of the dithio acid structure have been made both in the heterocyclic ring and in the nature of the amine moiety in III. Use of 2,6-dimethylpyridine resulted in the condensation with carbon disulfide on both active methyls to give IV. Use of 2-methylpyridine to give the anticipated N-methylpyridinium-2-dithioacetic acid in aqueous NaOH had previously been found (1) to result in replacement of the 2-methyl to give the pyridinium dithioacetic acid (V). This reaction is currently being run with the use of strong bases in non-aqueous media to give the desired compound VI or derivatives.



I



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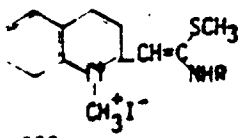

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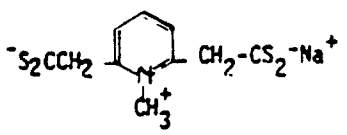

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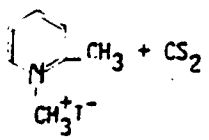
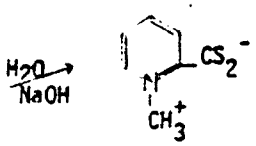
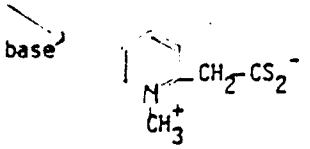


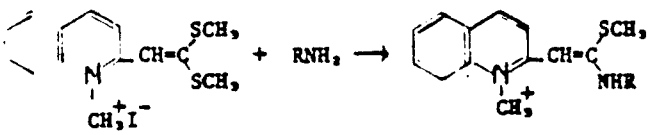


V



VI

The quinolinium methylthio amino derivatives (III) showed the best protective activity in this series of compounds, and at remarkably low dosage levels (9.38 mg/kg for the morpholino derivative and 2.34 mg/kg for the piperidino derivative). Testing data for these compounds are listed in Table 1. Other amines have been used to react with the bis(methylthio) quinolinium compound II, giving compounds of structure III. Use of one amine, $NH_2CH_2CH_2N(CH_3)_2$, resulted in replacement of both methylthio moieties.



a. $R=CH_2CH_2OCH_3$
b. $R=CH_2CH_2CH_2OH$

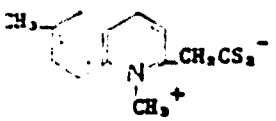
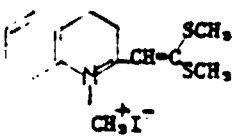
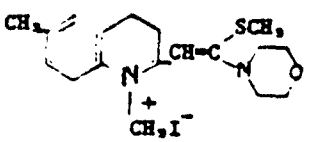
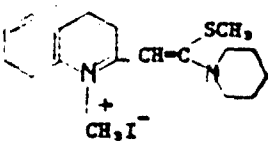
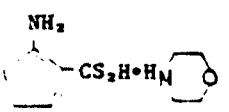
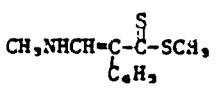
Other poly functional aliphatic amines are currently being substituted in the quinolinium dithioacetic acid structure, including those with 2 or 3 amine groups, hydroxy amines, mercapto amines, and piperazine derivatives to give other examples of III more closely allied to the more highly protective of the amino thiols.

Substituents in the 6-position of the quinoline ring were found to improve the antileukemic activity of the quinolinium dithioacetic acid zwitterions (I) (2) but not the activity of the bis(methythio) (II) or methylthio amino (III) derivatives (3,4). To determine the effect of a 6-substituent on the radioprotective activity of the quinolinium dithioacetic acid derivatives, the 6-methoxy derivative of the bis(methylthio) derivative (II) has been prepared.

Aminocycloalkenedithio Acids

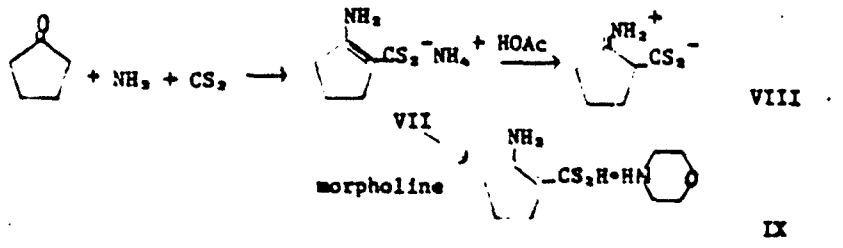
Dithio acid VIII and its ammonium (VII) and morpholinium (IX) salts have been prepared following a literature method (5). The ammonium salt was obtained in much lower yield than reported (15% vs. 80%), and attempts at recrystallization resulted in decomposition. Two simple modifications, use of a large

Table I. Radioprotector Screening Data

Compound	Route	Dose, mg/kg	LD_{50}/10d	Toxic deaths	Per cent survival[a]
	IP	150	~ 225	0/10	10
		75		0/10	20
		37.5		0/10	10
	PO	1200		0/10	0
		600		0/10	0
		300		0/10	0
	IP	150	~ 300	0/10	60
		75		0/10	0
		37.5		0/10	0
	PO	300		1/10	0
		150		2/10	10
		75		0/10	10
	IP	9.38	~ 15	0/10	60
		4.69		0/10	0
		2.34		0/10	0
	IP	4.69	~ 5	8/10	10
		2.34		0/10	70
		1.17		0/10	30
	PO	18.75		0/10	0
		9.37		0/10	0
		4.69		0/10	0
		2.34		0/10	0
	IP	300	~ 450	0/10	0
		150		0/10	0
		75		0/10	0
	IP	600	> 600	0/10	10
		300		0/10	40
		150		0/10	20

a A radiation dose of 100 rads was used 30 minutes after dosing. Animals were observed for a period of 30 days to determine survival.

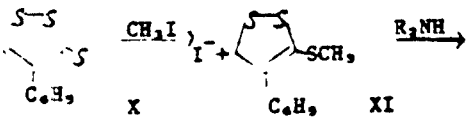
excess of carbon disulfide and ethyl acetate as purification solvent, resulted in a marked improvement in yield (49%). Both VIII and IX have been submitted for screening. Testing data have been received for IX, which gave no protection to mice vs. 1000 rad.

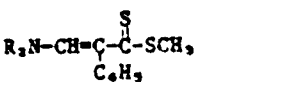


It is of interest to note that compound IX showed a strong peak for SH in the infrared spectrum at ∿ 2500 cm^{-1}. The imino dithio acid VIII, however, gave no peak for SH absorption. It is possible that VIII is mainly the immonium dithio acid zwitterion, whereas IX may have an appreciable amount of the free acid, which is hydrogen bonded to morpholine.

Reaction of Dithiolethiones with Amines

The preparation of 3-dialkylamino-2-aryldithiopropenoates (XII) has been reported (6). This reaction has been utilized to prepare the primary (XIII) and secondary amine (XIV) analogs.





XII	R= CH_3
XIII	R= H
XIV	R= CH_3, H
XV	R= morpholine

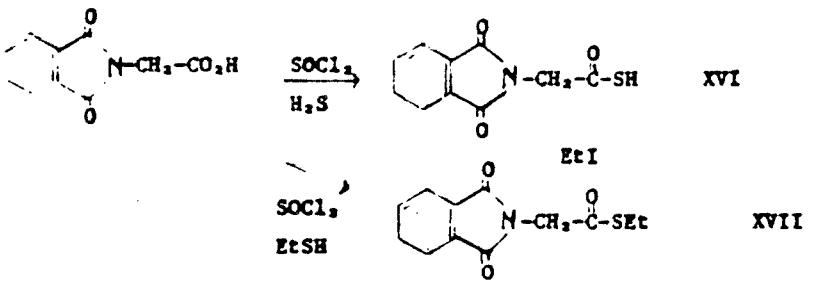
The primary amine adduct XIII proved to be too unstable for testing, but the methylamino (XIV), dimethylamino (XII), and morpholino (XV) adducts have been submitted for screening. Test results have been received for the methylamino derivative XIV, which gave up to 40% protection to mice vs. 1000 rad.

The reaction of N-aminomorpholine with the methylated 4-phenyldithiole-3-thione gave a product having two aminomorpholine moieties in the molecule. Reaction with guanidine gave an oil which has not been characterized. The use of alkyl-substituted guanidines in this reaction is currently being investigated to provide solid products.

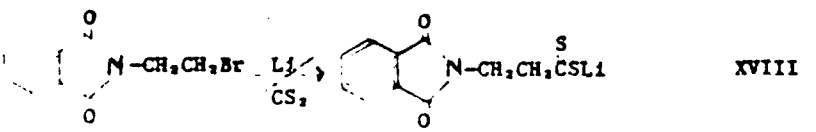
Both precursors X and XI have also been sent for screening, since aryldithiole-3-thiones have been found to raise glutathione levels in animal cells (7). Increased glutathione levels have been shown to provide protection to mice against hepatotoxic agents, and have been postulated to be of value in radiation protection (7).

Phthaloylaminoalkanedithio Acids

Attempts to prepare phthaloylaminoalkyldithio acids produced thiol acid XVI as its ethyl ester XVII. It was not found possible to remove the phthaloyl group without destruction of the thiol acid moiety.

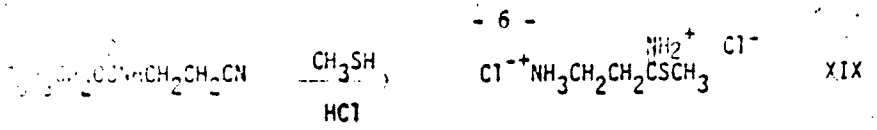


Reaction of N-(2-bromoethyl)-phthalimide with lithium and carbon disulfide also failed to give the desired dithio acid XVIII.

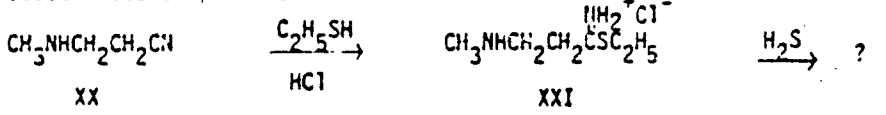


Conversion of Aminonitriles to Dithio Acids

It was found previously (8) that reaction of a carbobenzoxy-aminopropionitrile with methanethiol in the presence of HCl provided an iminoester hydrochloride (XIX).



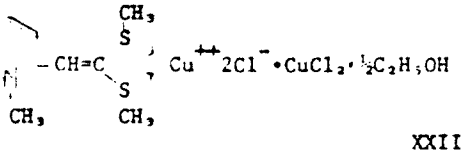
Attempts to convert this and the phenyl ester to the dithio acid were not successful, however. Use of the unblocked aminopropionitrile XX also resulted in the formation of an iminoester XXI, but reaction with hydrogensulfide gave a product whose composition was not determined.



Metal Complexes of 2-Bis(2-methylthio)vinyl-1-methyl-quinolinium Iodide

Since dithio acids or derivatives are potentially strong complexing agents for copper ion, the possibility exists that compounds of types I-III may act as mimics of superoxide dismutase, a copper-containing enzyme. A relatively simple copper complex of a disubstituted salicylic acid has been reported tocatalyze the disproportion of superoxide (9) and thus be a possible radiation protector. To test this possibility, a copper (II) complex of II was prepared by a graduate student and submitted for screening. In the event that compounds of this type act as mimics of superoxide dismutase, then the copper complex should have greater radiation protective activity than II.

The isolated complex was most likely an oligomer, since elemental analysis indicated a structure having two copper ions per molecule of II. Structure XXII is proposed on the basis of the analysis and IR bands for Cu-S at 500 and 575 cm^{-1} and a Cu-Cl band at 400 cm^{-1}.



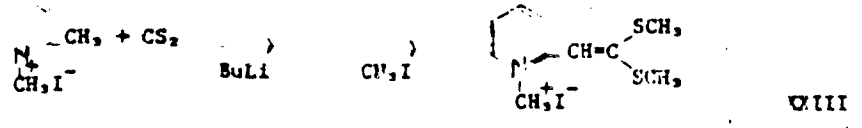
XXII

Potentiometric titration of II in the presence of Cu(II) indicated the formation of a 2:1 copper complex (in alkaline solution) having a stability con-

stant of 10^{11}, which is sufficiently high for the complex to exist under cellular conditions. Fe(III), Al(III), and Zn(II) ions are also being measured for their ability to complex with II as well as with an example of III.

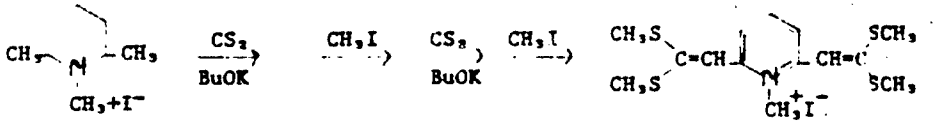
Pyridinium-2-dithioacetic Acid Derivatives

Whereas N-methylpicoline did not condense with carbon disulfide in the presence of aqueous sodium hydroxide to give the desired dithioacetic acid zwitterion (VI), but gave V instead, the bis(methylthio) derivative of VI (compound XXIII) has been obtained by the use of n-butyl lithium in tetrahydrofuran. No attempt was made to isolate the dithio acid, because of the previously observed instability of the acid.



XXIII

Attempts to prepare the tetrakis(methylthio) derivative (XXIV) of the bis-(dithioacid) derivative of lutidine (IV) by the usual procedure have not given a complete conversion to the tetrakis(methylthio) compound. The use of a two-step procedure, using K t-butoxide as base, is providing a more complete conversion, however.



XXIV

Use of K t-butoxide as a base for the condensation of carbon disulfide with N-methylpicolinium iodide has given a condensation product, XXV, which was converted to XXIII on methylation with methyl iodide. This shows further the difference between the active methyl of pyridine and the active methyl of quinoline for CS_2 condensations.

XXV

Compounds submitted for radiation-protective screening are listed in Table II.

Experimental

Ammonium 2-Aminocyclopentene-1-dithiocarboxylate (VII)

Cyclopentanone (25.14g, 0.30 mole) and carbon disulfide (25 ml, 0.42 mole) were added to 300 ml of concentrated aqueous ammonia at 0°. Stirring was continued for 4 hr, and the mixture was stored in the freezer overnight. The orange solid was filtered and washed with ether, giving 13.65g (26%) of a yellow solid, mp 120-121° dec (lit (5) mp 135-137°).

2-Iminocyclopentanedithiocarboxylic Acid (VIII).

Ammonium salt VII (7.48g) was dissolved in 50 ml of glacial acetic acid at 70°. When all the solid was in solution, water (50 ml) was added, and the yellow suspension was cooled in ice. Filtration gave 5.67g of an orange solid, which was recystallized from DMF-water, yielding 3.51g of VIII, mp 95-96° (lit (5) mp 96°). A second crop (1.57g) gave a total yield of 78%.

Morpholinium 2-amino-1-cyclopentene-1-dithiocarboxylate (IX)

The ammonium salt (VII (0.50g) was suspended in 5 ml of morpholine and heated at 50° with stirring for 2 hr. The yellow material gradually became orange-brown. Cooling to room temperature, followed by filtration, washing with ether, and recrystallization from methanol, provided 0.26g (37%) of orange needles, mp 137-140° (lit (5) mp 157-162°).

Table II. Compounds Submitted for Screening

Code No. 0942

Compound	Structure	Wt.,g	Reference
2-Iminocyclopentane-1 dithiocarboxylic acid	VIII	3.0	T. Takeshima et al., J. Org. Chem., 34, 730 (1969).
Morpholinium 2-amino-1-cyclopentenedithiocarboxylate	IX	2.5	Ibid. (for NH_4^+ salt)
4-Phenyl-1,2-dithiole-3-thione	X	2.1	E.K. Fields, J. Amer. Chem. Soc 77, 4255 (1955).
4-Phenyl-1,2-dithiole-3-thione methiodide	XI	2.1	Ibid.
Methyl 3-methylamino-2 phenyl-dithiopropenoate	XIV	2.7	G. LeCoustumer and Y. Mollier, Bull. Soc. Chim. Fr., 2958 (197
Methyl 3-morpholino-2-phenyl dithopropenoate	XV	2.1	Ibid.
Methyl 3-dimethylamino-2-phenyl-dithiopropenoate	XII	2.1	Ibid.
Sodium 1-methylpyridinium 2,6-bis(dithioacetate) zwitterion	IV	2.5	W. Foye et al., J. Pharm . Sci. 67, 962 (1978).
1-Methyl-2-(2-methylthio-2-(2-methoxyethylamino)vinyl)-quinolinium iodide	IIIa	2.0	Quart. report, April-June, 1984
1-Methyi-2-(methylthio-2-(3-hydroxypropylamino(vinyl)-quinolinium iodide	IIIb	2.0	Ibid.
1-Methyl-2-(2-bis(dimethylamino-ethylamino)vinyl)-quinolinium iodide		2.0	Ibid.
6-Methoxy-1-methyl-2-bis-(2-methylthio)-vinyl quinolinium iodide	II(6-OCH_3)	2.1	W. Foye and J. Kauffman, J. Pha Sci., 69, 477 (1980)
1-Methyl-2-bis(2-methylthio) vinyl -quinolinium iodide Cu(II) complex	XXII	2.2	Quart. Report, April-June, 1984

4-Phenyl-1,2-dithiole-3-thione (X). A mixture of 24.02g (0.20 mole) of cumene, 9.60g (0.30 mole) of sulfur, and 0.10g (0.42 mmol) of di-o-tolylguanidine was held at reflux for 9 days, then placed in a freezer for a few hours. The dark red solid was filtered and recrystallized from benzene, affording 5.10g (48%) of a red-brown solid, mp 121-122.5° (lit (10) mp 122°).

4-Phenyl-1,2-dithiole-3-thione methiodide (XI). A mixture of 4.00g of X, 12ml of methyl iodide, and 40 ml of n-propyl acetate was stirred and heated at reflux for 4.5 hr, and stirred at room temperature for 18 hr. The resulting solid was filtered and washed with ethyl acetate, yielding 6.51g (97%) of a brown powder, mp 173-174° dec (lit (10) mp 194° dec).

Methyl 3-methylamino-2-phenylpropenedithiocarboxylate (XIV). To a suspension of 1.00g of XI in 30ml of benzene was added 1ml of a 40% aqueous solution of methylamine. After being stirred vigorously for 15 min., the aqueous phase was removed, and the benzene solution was dried (Na_2SO_4). Removal of solvent gave a dark yellow solid which was purified by column chromatography (alumina) to produce 0.49g (83%) of orange crystals, mp 128-132°. The NMR spectrum indicated approximately a 1:7 mixture of E and Z isomers. IR(KBr): 1620 (c=c), 1250 (c=s), 930 (c=s) cm^{-1}. NMR($CDCl_3$): δ 2.5(CH_3), 3.0-3.2(NCH_3), 6.8-7.0(CH), 7.2-7.4(arom H).

Anal. Calcd. for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.86; N, 6.27.
Found: C, 59.21; H, 5.98; N, 5.81.

Methyl 3-morpholino-2-phenylpropenedithiocarboxylate (XV). Morpholine (0.50ml, 5.74 mmol) was added to a stirred suspension of 1.00g (2.84 mmol) of 4-phenyl-1,2-dithiole-3-thione methiodide (XI) in 25ml of benzene. Stirring was continued for 1 hr, and the solid morpholine hydroiodide was filtered and washed with benzene. Removal of solvent from the combined filtrates was followed by column chromatography (alumina) and recrystallization from benzene-hexanes to give 0.51g (65%) of yellow-orange crystals, mp 127-

129°. IR (KBr): 1565 (c=c), 1235 (c=s), 910 (c=s) cm^{-1}. NMR ($CDCl_3$): δ 2.60 (SCH_3), 3.07 (CH_2NCH_2), 3.53 (CH_2OCH_2), 7.32 (arom H), 8.43 (CH=C).

Anal. Calcd. for $C_{14}H_{17}NOS_2$: C, 60.18; H, 6.13; N, 5.01. Found: C, 59.99; H, 6.06; N, 4.94.

Methyl 3-dimethylamino-2-phenylpropenedithiocarboxylate (XII). To a stirred suspension of 8.00g (22.7 mmol) of XI in 150 ml of benzene was added 8.30g (46.0 mmol) of 25% aqueous dimethylamine. After being stirred for 15 min, the aqueous phase was removed, and the organic phase was dried (Na_2SO_4), filtered, and stripped of solvent. The brown powder was chromatographed over silica and recrystallized from benzene, giving 2.67g (49%) of orange crystals, mp 149-151° (lit (6) mp 153°). IR(KBr): 1580 (c=c), 1275 (c=s) cm^{-1}. NMR ($CDCl_3$): δ 2.60 (SCH_3), 2.80 ($N(CH_3)_2$), 7.33 (arom H), 9.35 (CH=C).

Ethyl phthaloylthioglycinate (XVII). To a suspension of 2.00g (9.75 mmol) of phthaloylglycine in 10 ml of benzene was added 7.0ml (96.0 mmol) of thionyl chloride. The mixture was refluxed for 2 hr, and the solvent was removed by distillation. Remaining thionyl chloride was removed by co-distillation with benzene (10ml) four times. Benzene (15ml) and pyridine (2.0ml) were added to the residue, and H_2S was bubbled into the solution for 2 hr. Ethyl iodide (5.0 ml, 62.5 mmol) was added, and the mixture was stirred overnight (R.T.), diluted with benzene, and filtered. The solid was washed with benzene and filtered, and the residue was washed with benzene until the washings were colorless. Evaporation of the combined benzene solutions gave 2.05g of yellow solid. Chromatography on alumina gave a white solid, mp 121-123.5° (previous mp (11) 122.5-123.5°).

Sodium 1-methylpyridinium-2,6-bis(dithioacetate) zwitterion (IV). To a solution of 2,6-dimethylpyridine methiodide (10.04g, 0.04 mole) in 25 ml of water was added 50ml of dioxane and 25 ml (0.416 mole) of carbon disulfide.

A solution of 15.0g of NaOH in 75 ml of water was added in portions over 1½ hr, and the reaction was stirred at room temperature for 37 hr. The red-brown product was filtered and washed with hot water. After drying, the product weighed 3.06g (26% yield); mp 232-236° (lit (1) mp 249-250°). IR(KBr): 1335 (c=s), 930 (c=s). NMR(DMSO-d6): δ 2.90 (CH_2), 4.0 (NCH_3), 7.6-8.0 (arom H).

Anal. Calcd. for $C_{10}H_{10}NNaS_4$: C, 40.65; H, 3.41; N, 4.74.
Found: C, 41.04; H, 3.46; N, 4.93.

1-Methyl-2-(2-methylthio-2-(2-methoxyethylamino)vinyl)-quinolinium iodide (III). To 3.0g (7.7 mmol) of II (2) was added 50 ml of dimethyl formamide and 0.58g (7.7 mmol) of 2-methoxyethylamine. The mixture was stirred at 40° for 3 days, was cooled, and was added portion wise to 400 ml of ether. The solution was stirred with cooling in an ice-bath, and the precipitate was filtered and dried. The crude product was recrystallized from 2-propanol-ethanol, giving 1.85g (58%) of yellow crystals, mp 143-145°. IR(KBr): 3210 (NH), 1610 (c=c), 1345 (SCH_3), 835 (c=c) cm^{-1}. NMR($CDCl_3$): δ 2.76 (SCH_3), 3.45 (OCH_3), 3.80 (CH_2CH_2), 4.00 (NCH_3), 5.62 (CH=C), 7.4-8.0 (arom H).

Anal. Calcd. for $C_{15}H_{20}IN_2OS$: C, 46.26; H, 5.08; N, 6.72.
Found: C, 45.91; H, 5.02; N, 6.38.

1-Methyl-2-(2-methylthio-2-(3-hydroxypropylamino)vinyl)-quinolinium iodide (III). To 3.0g (7.7 mmol) of II (2) was added 50 ml of dimethylformamide and 0.58g (7.7 mmol) of 3-aminopropanol. The solution was stirred at 40°for 3 days, was cooled, and was added to 400 ml of ethyl acetate. The gummy residue turned greenish yellow in the refrigerator, and then stood at room temperature for several hr. The precipitate was filtered and dissolved in abs. ethanol; addition of ether gave 1.3g (40% yield) of a green-yellow solid; mp 135-138°, IR(KBr): 3220 (NH), 1620 (c=c), 820 (c=c) cm^{-1}. NMR DMSO-d6): δ 1.6-2.0 (CH_2), 2.6 (SCH_3), 3.2-3.6 (NCH_2, OCH_2), 4.0 (NCH_3), 5.4 (CH=C), 7.6-8.2 (arom H).

Anal.-Calcd. for $C_{16}H_{21}IN_2OS$: C, 46.16; H, 5.08; N, 6.72.
Found: C, 45.81, H, 5.11; N, 6.49.

1-Methyl-2-bis(2-dimethylaminoethylamino)vinyl-quinolinium iodide. To 3.0g (7.7 mmol) of II (2) was added 50 ml of dimethylformamide and 1.35g (1.54 mmol) of unsym-dimethylethylenediamine. The solution was heated at 70° for 2 hr, and stirring was continued at 35° for 3 days. After being cooled, the mixture was added to 350 ml of ether, and a yellow precipitate was filtered and dried. The crude product was dissolved in 15ml of DMF, filtered, and added to 100 ml of ether. Yellow crystals were isolated and oven-dried, giving 1.35g (37% yield) of green-yellow powder, mp 148-150°. IR(KBr): 3210 (NH), 1605 (c=c) cm^{-1}. NMR(DMSO-d6): δ 2.20 ($2N(CH_3)_2$), 3.2-3.6 ($2CH_2CH_2$), 7.4-7.7 (arom H).

Anal.-Calcd. for $C_{20}H_{32}IN_5$: C, 51.17; H, 6.87; N, 14.92.
Found: C, 51.01; H, 6.88; N, 14.78.

1-Methyl-2-bis(2-methylthio)vinylpyridinium iodide. To a solution of 2-picoline (0.93g, 0.01 mole) in dry tetrahydrofuran (15ml) under nitrogen at 0° was added a solution of n-butyl lithium (4.4ml, 2.5M) in hexane, and the resulting solution was stirred for 30 min. To the red solution was added carbon disulfide (1.2 ml) in tetrahydrofuran (5ml) dropwise at 0°, and a red solid precipitated. After the mixture stood at 0°for 30 min, an excess of methyl iodide (4ml) was added; a clear red solution slowly formed. It was stirred overnight (R.T.), and was taken up in methylene chloride (40ml) and repeatedly washed with water until the washings were colorless. The aqueous layer was concentrated to 20-30 ml and stored at 0°. A yellow solid was filtered and recrystallized from water; mp 134-135°. NMR($CDCl_3$): δ 2.56 (s, 3H, SCH_3), 2.67 (s, 3H, SCH_3), 4.56 (s, 3H, NCH_3), 6.57 (s, 1H, CH=C), 7.5-8.6 (m, 3H, arom), 9.0-9.6 (d, 1H, arom).

1,2-Dimethyl-6-methoxyquinolinium iodide. A mixture of 14.6g (84.2 mmol) of 6-methoxyquinaldine (12) and 6.6 ml (106 m mol) of methyl iodide in a 1000 ml

flask was cooled in an ice bath for 1 hr, kept at room temperature for 1 hr, and heated at 65° for 15 hr. The product was recrystallized from 300 ml of 95% ethanol, providing 16.9g (63% yield) of yellow-green needles, mp 229-231° dec (lit (12) mp 235-238° dec).

6-Methoxy-1-methyl-2-bis(2-methylthio)vinylquinolinium iodide. A mixture of sodium hydride (2.00g of a 60% dispersion in mineral oil, 50 mmol) in 180 ml of dry 2-propanol was cooled in ice and treated with 15.8g (50.1 mmol) of 1,2-dimethyl-6-methoxyquinolinium iodide. The mixture was stirred at 0° for 15 min, and 10 ml (166 mmol) of carbon disulfide was added, producing a red-violet suspension which was stirred for 17 hr (R.T.). The mixture was treated with 10 ml (161 mmol) of methyl iodide, stirred 2 hr (R.T.) and filtered, and the solid was washed with four 50 ml portions of toluene. Drying in vacuo produced 16.19g of brown powder, mp 200-203° dec, which was recrystallized from 500 ml of water (cooling only to room temperature) to give 4.64g (22%) of dark red powder, mp 212-214° dec (lit (3) mp 222-225° dec). IR(KBr): 1265 (CH_2S), 1020 (CH_3S), 830 (CH=C)cm^{-1}. NMR(DMSO-d6): δ 2.58 (s, 3H, SCH_3), 2.73 (s, 3H, SCH_3), 4.07 (s, 3H, OCH_3), 4.47 (s, 3H, NCH_3), 6.78 (s, 1H, CH=C), 7.67-9.07 (m, 5H, arom H).

1-Methyl-2-dithioacetylidene-1,2-dihydropyridine (XXV).

To a suspension of 1,2-dimethylpyridinium iodide (2.35g, 0.01 mole) in dry toluene (15 ml) was added potassium t-butoxide (2.4g, 0.02 mole) and 5 drops of 95% ethanol. The mixture was stirred under nitrogen for 15 min., and the yellow solution was decanted into a dry flask. This process was repeated 5-6 times, and the solution was dried (Na_2SO_4) and filtered. To the filtrate was added a large excess of carbon disulfide, and an orange-red precipitate appeared. After being stirred for 10 min, it was filtered, washed with toluene, and dried under vacuum; mp 130-135°. NMR (DMSO-d6): 3.33 (s, 3H, NCH_3), 4.23 (s, 1H, CH=), 7.8-8.4 (m, ring H).

Reaction of the product with carbon disulfide in methylene chloride gave a compound identical with XXIII.

Anal. Calcd. for $C_{10}H_{14}NS_2$: C, 35.40; H, 4.16; N, 4.12.
Found: C, 35.26; H, 4.11; N, 4.19.

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